

Polycystic ovary syndrome

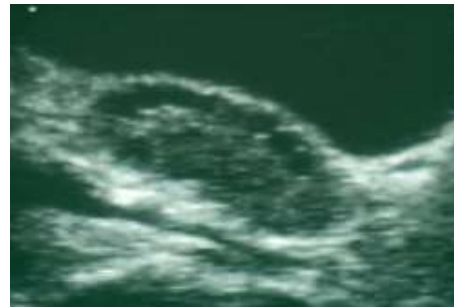
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Polycystic ovary syndrome: prevalence, presentation and investigations

- Presentation, prevalence and diagnostic criteria
- Endocrine and metabolic features
- Investigation
- Common management issues



Polycystic ovary syndrome

- Characterised by anovulation with clinical (hirsutism/acne) and/or biochemical evidence of androgen excess
- Clinical, endocrine and metabolic phenotype is heterogeneous and is affected by ethnicity and environment
- Typically presents during adolescence
- Affects >5% women of reproductive age
- Commonest cause of menstrual dysfunction (>80% cases of anovulatory infertility) and hirsutism
- Typical endocrine features are raised testosterone and LH
- Also associated with metabolic abnormalities and increased risk of type 2 diabetes

Polycystic ovaries and polycystic ovary syndrome

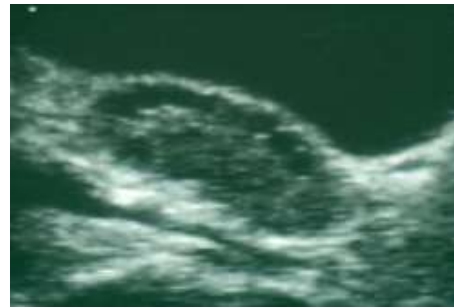
- Polycystic ovaries (PCO): morphological appearance of ovaries in women who may either be symptomatic or asymptomatic
- Polycystic ovary syndrome (PCOS): PCO plus a symptom or sign
- Most consistent biochemical abnormality is elevated serum testosterone (may be present even in asymptomatic women)

What causes polycystic ovary syndrome?

- We don't know for sure
- Genetic causes are very important
- Being overweight makes things worse
- Identification of the key genes will help enormously in:
 - Diagnosis
 - Prognosis for fertility and long-term health
 - Planning treatment

Polycystic ovary syndrome: prevalence, presentation and investigations

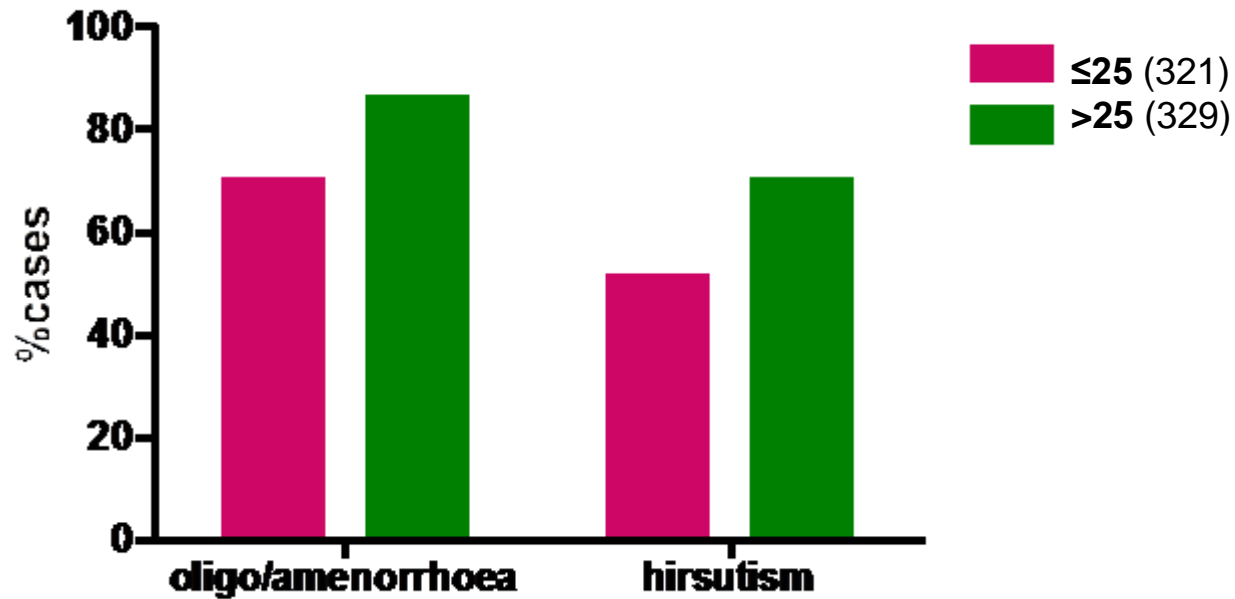
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Presentation of polycystic ovary syndrome

- Classic presentation is with symptoms of **anovulation** (amenorrhoea, oligomenorrhoea, irregular cycles) associated with symptoms (hirsutism, acne, alopecia) and/or biochemical evidence of **hyperandrogenism**
- However spectrum of presentation includes anovulatory women without hirsutism and hirsute women with regular cycles (“Rotterdam” diagnostic criteria: *Hum Reprod*, 2004 19 1-7)

Overweight/obese women with PCOS are more symptomatic



Prevalence of PCO and PCOS

- PCO in 20-25% of “normal” (mainly European) population but higher in populations of south Asian origin

(Polson et al, *Lancet* 1988 1(8590):870-2; Clayton et al, *Clin Endocrinol* 1992 37:127-34; Rodin et al, *Clin Endocrinol* 1998, 49:91-9)

- PCOS (*NIH definition*) in 4-8% of “unselected” population of white and black subjects

(Knochenhauer et al, *J Clin Endocrinol Metab*, 1988 83:3078-82)

Diagnostic criteria for PCOS

NIH 1990

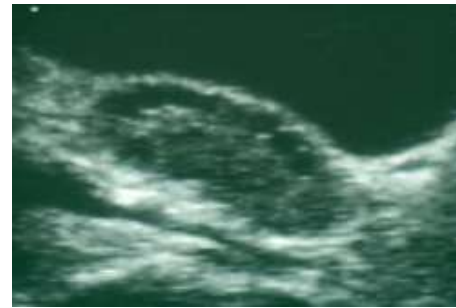
- Chronic anovulation
- Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other aetiologies, eg CAH)
(both criteria needed)

Rotterdam 2003

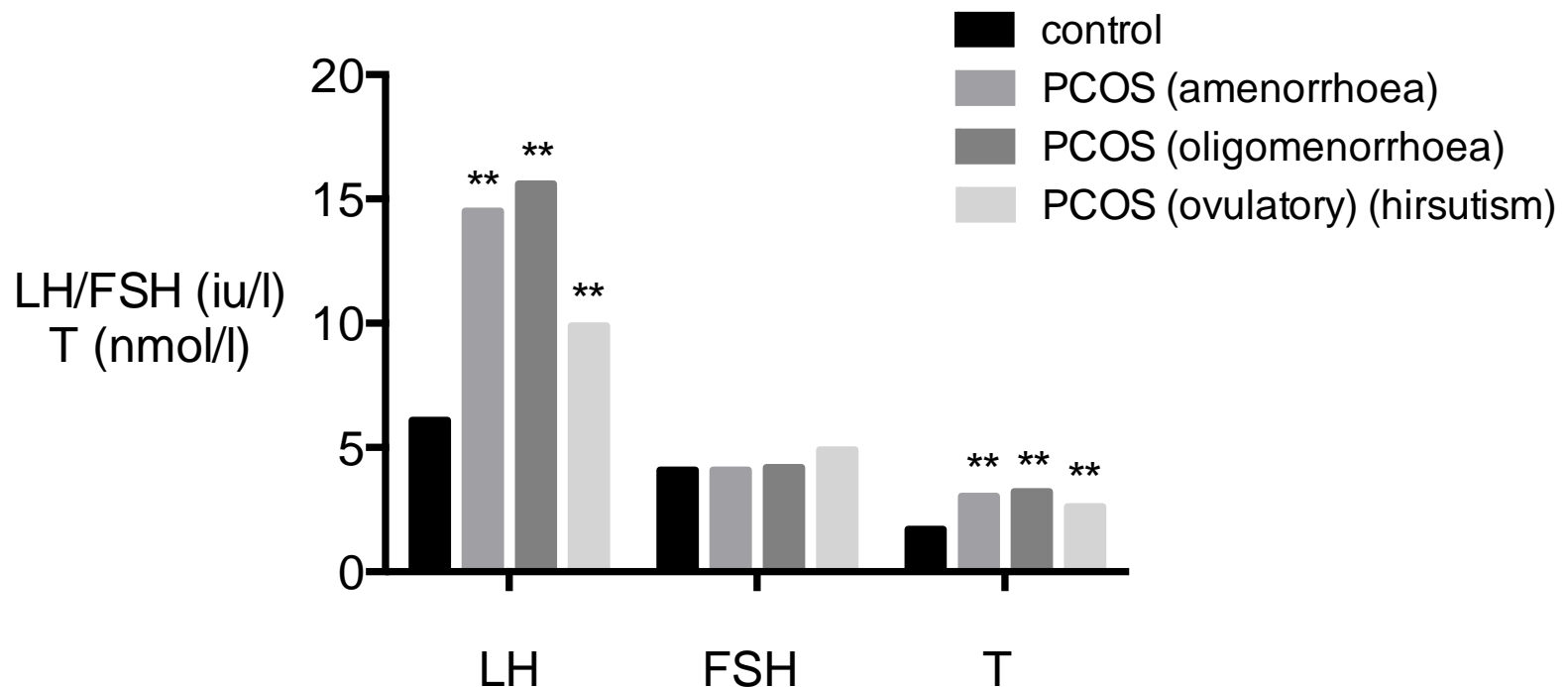
- Oligo- and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries
(2 of 3 criteria needed)

Polycystic ovary syndrome: prevalence, presentation and investigations

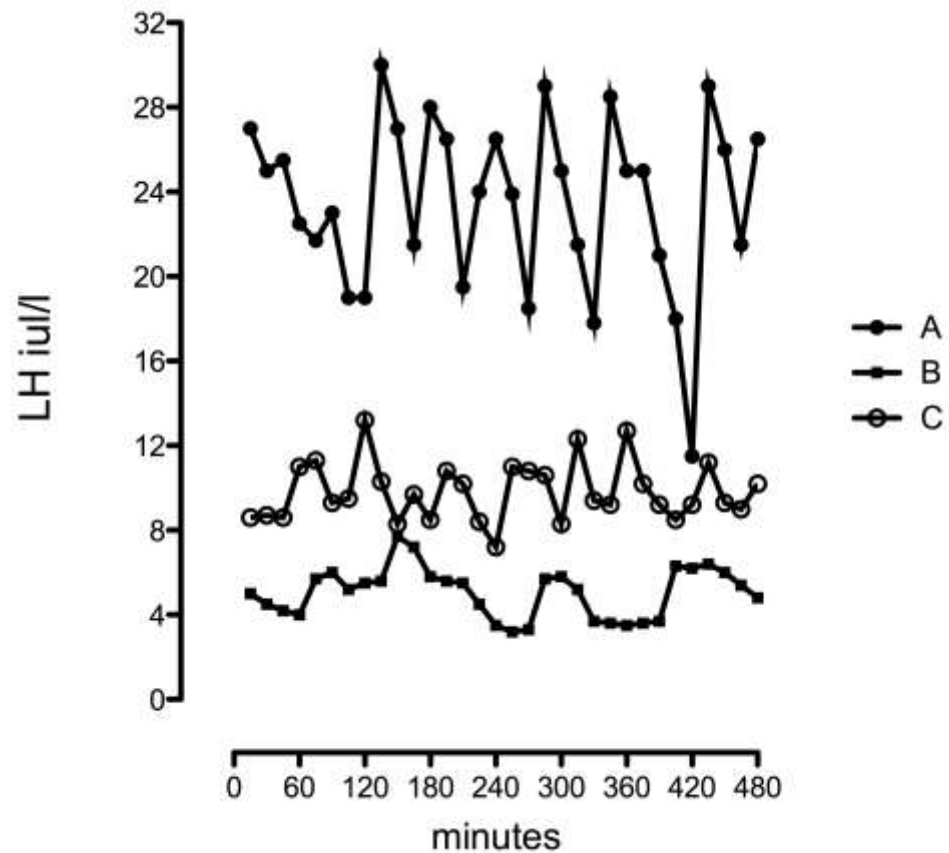
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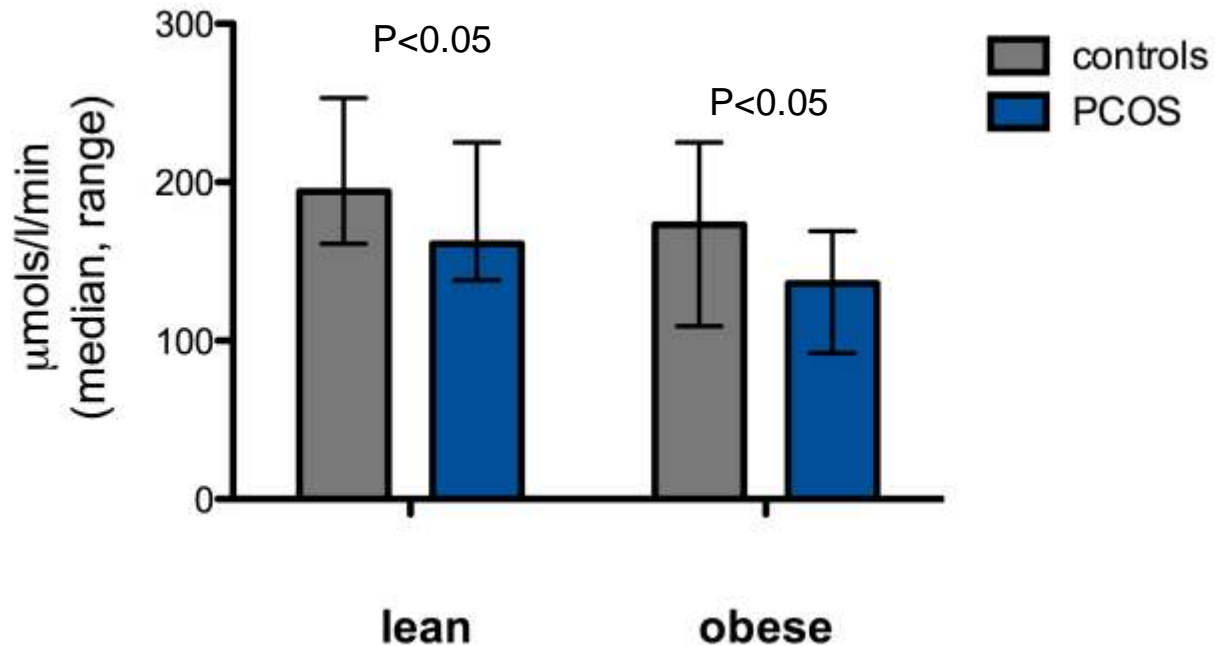
Elevated LH and testosterone in women with PCOS



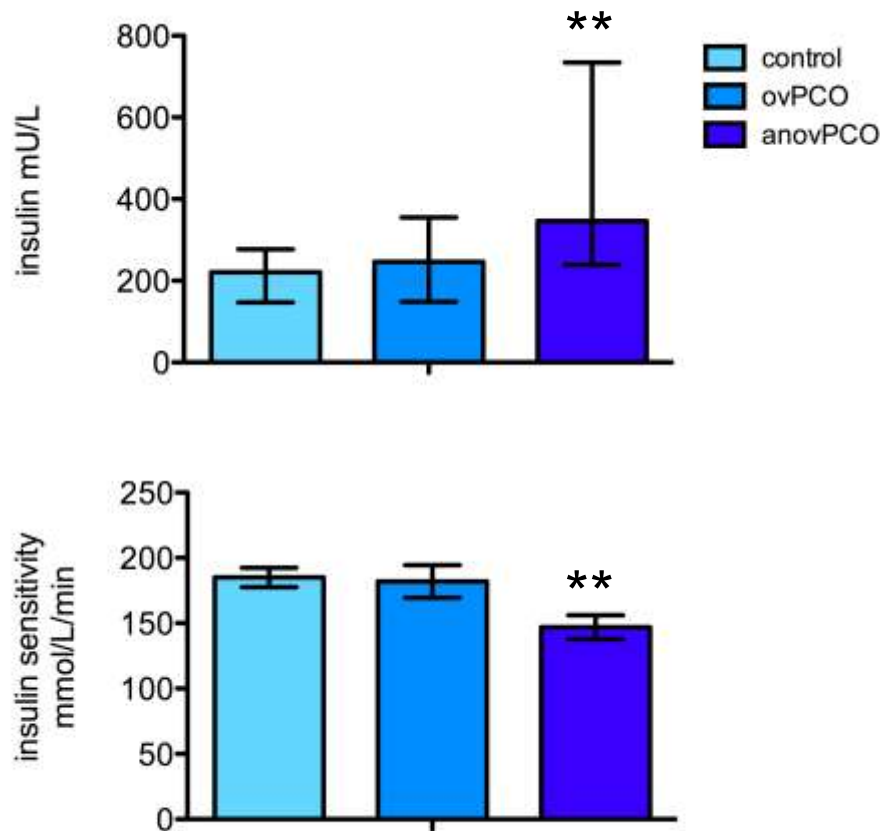
Variable LH secretion in women with PCOS



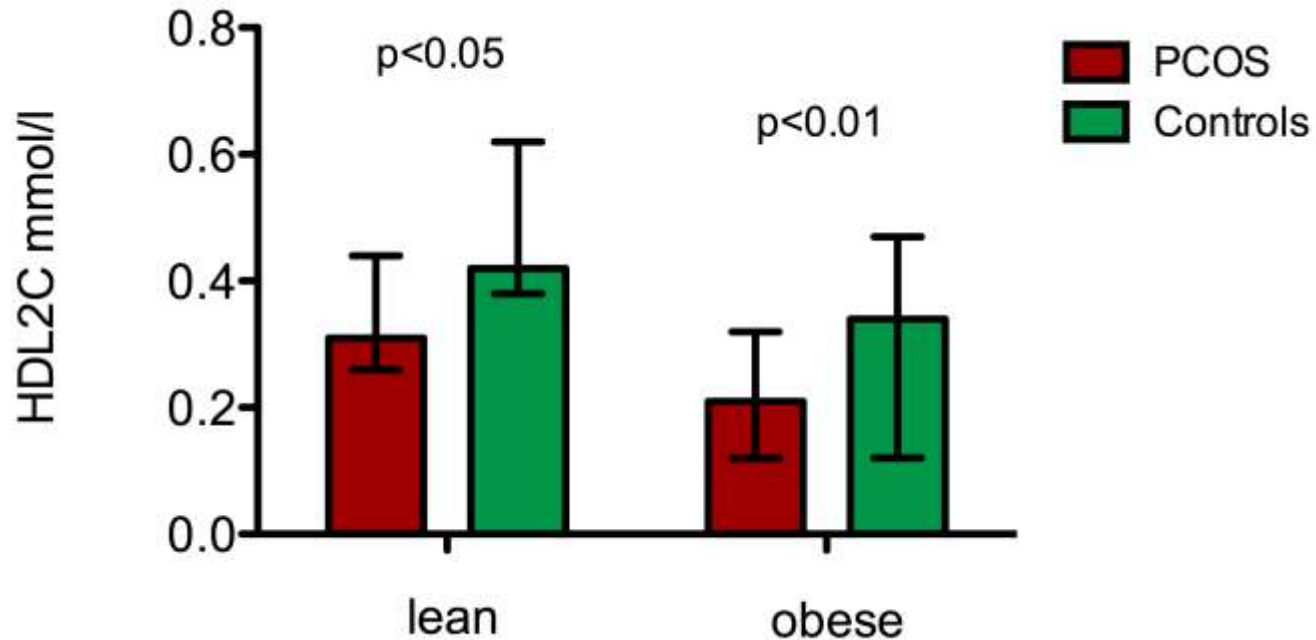
Insulin sensitivity is reduced in lean and obese women with PCOS



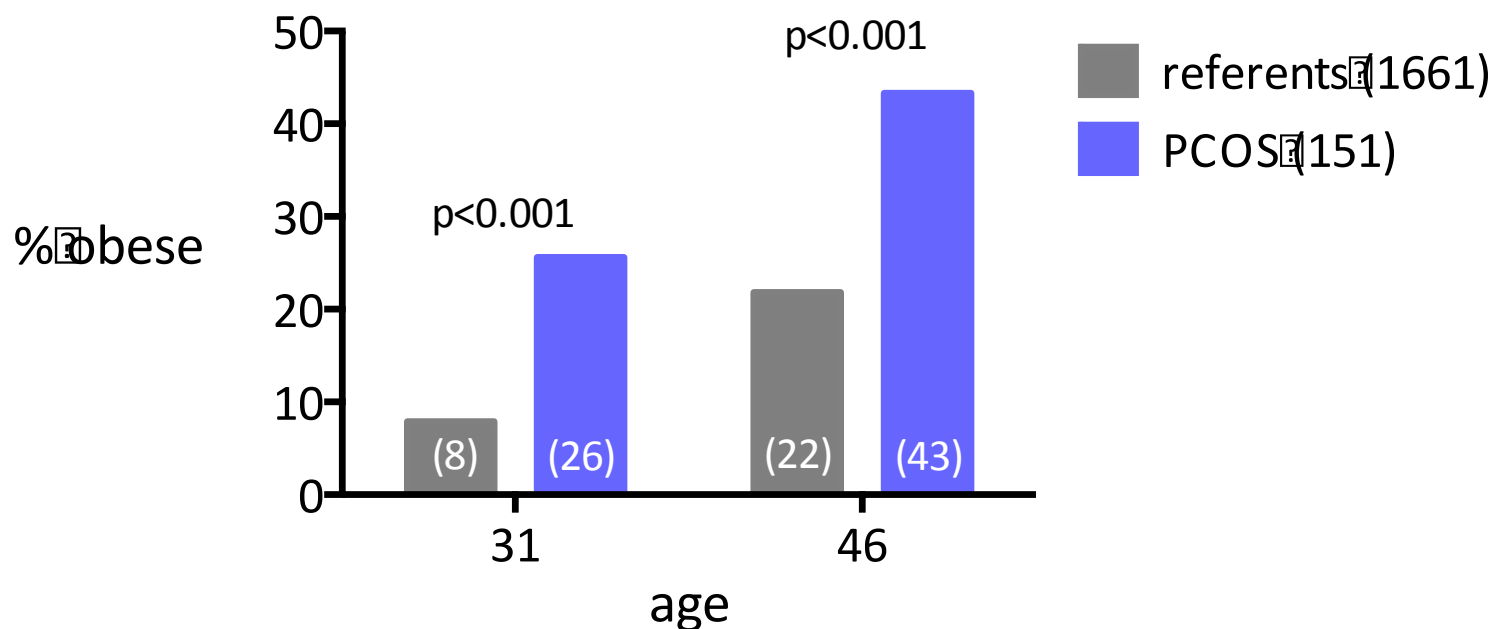
Hyperinsulinaemia and insulin resistance in PCOS is related to menstrual cycle



HDL2-Cholesterol is reduced in lean and obese women with PCOS



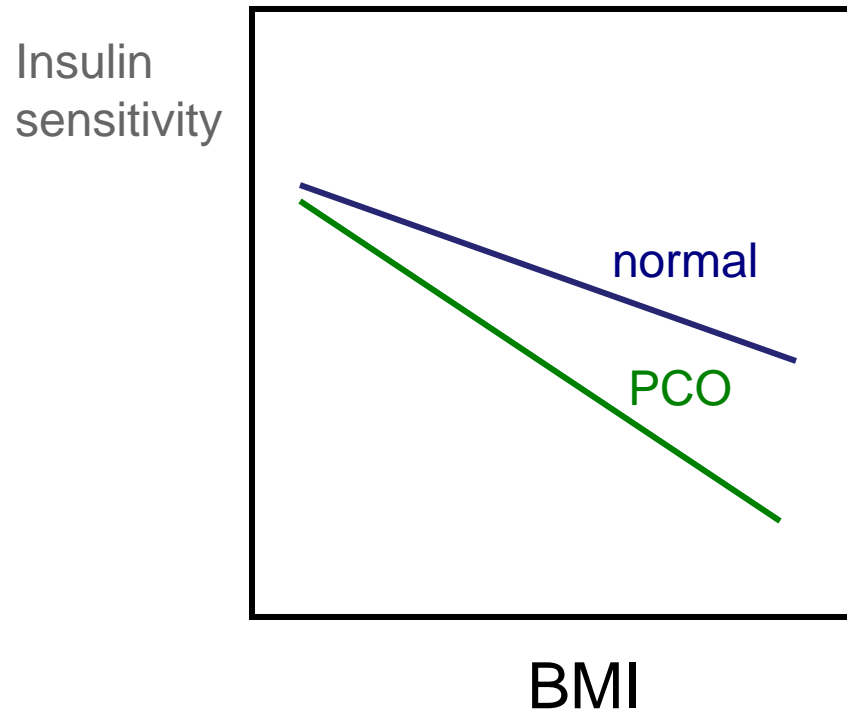
Women with PCOS* are more obese than age-matched controls at 31 and 46 years



Data from North Finland Birth Cohort study (Ollila *et al*, JCEM 2016 101 739-47)

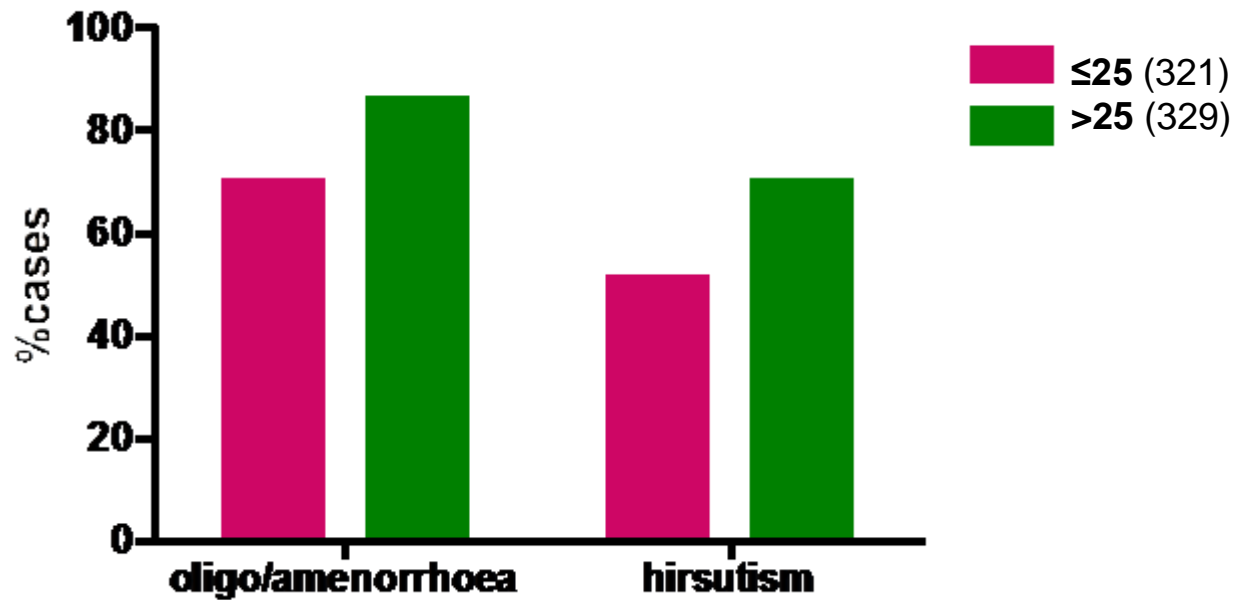
* PCOS women had both oligomenorrhoea and hyperandrogenism

Obesity amplifies insulin resistance in women with PCOS



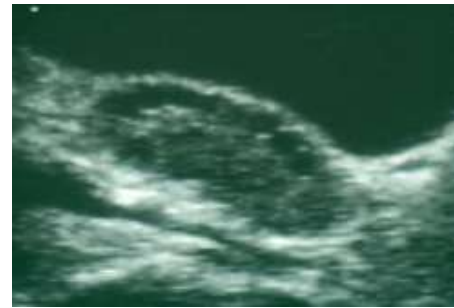
(Adapted from Holte *et al*, *J Clin Endocrinol Metab* 1994, 78 1052)

Overweight/obese women with PCOS are more symptomatic than lean PCOS subjects



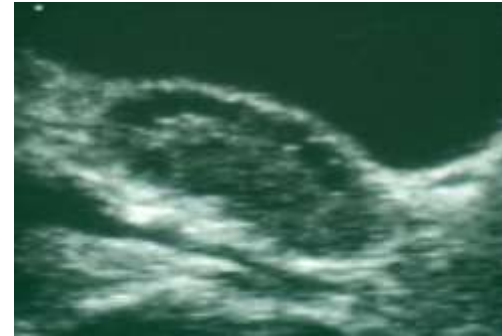
Polycystic ovary syndrome: prevalence, presentation and investigations

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- **Investigation**
- Common management issues



Diagnosing polycystic ovary syndrome

- History: irregular, infrequent or absent periods with hirsutism, acne, alopecia
- Examination: weight and height (BMI), excess body hair
- Blood tests: raised testosterone and LH levels in blood; glucose levels in obese subjects
- Scan: typical appearance of ovaries on ultrasound



Investigation of PCOS

These tests complement clinical diagnosis

- Oligo/amenorrhoea
- Hirsutism
- Obesity (BMI >30)
- LH, FSH, (prolactin, estradiol) TFTs
- Testosterone or androstendione
- OGTT

SHBG, Free T, DHEAS, 17-OHP, insulin - NOT routinely needed

Investigation of hirsutism

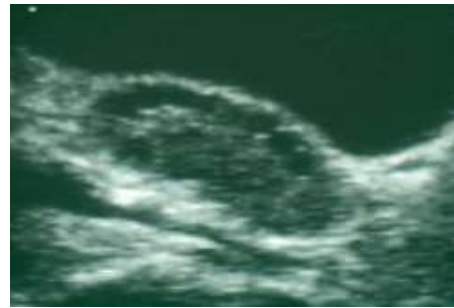
- mild, chronic hirsutism, regular cycles
- moderate hirsutism and/or cycle disturbance
- severe hirsutism, short history, testo >5 nmol/l
- no tests? (testo, US)
- testo, US, (LH, FSH)
- DHEAS, 17OHP
dexamethasone suppression
24h urine free cortisol
ovarian &/or adrenal imaging
fasting glucose/insulin

Endocrine evaluation and classification of patients with hirsutism: summary

- Polycystic ovary syndrome and idiopathic hirsutism account for the vast majority of cases
- Endocrine evaluation usually requires only a small number of investigations
- Total testosterone (or androstenedione) is the most useful screening test

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Management of PCOS

Treat presenting complaint

Think about long-term consequences

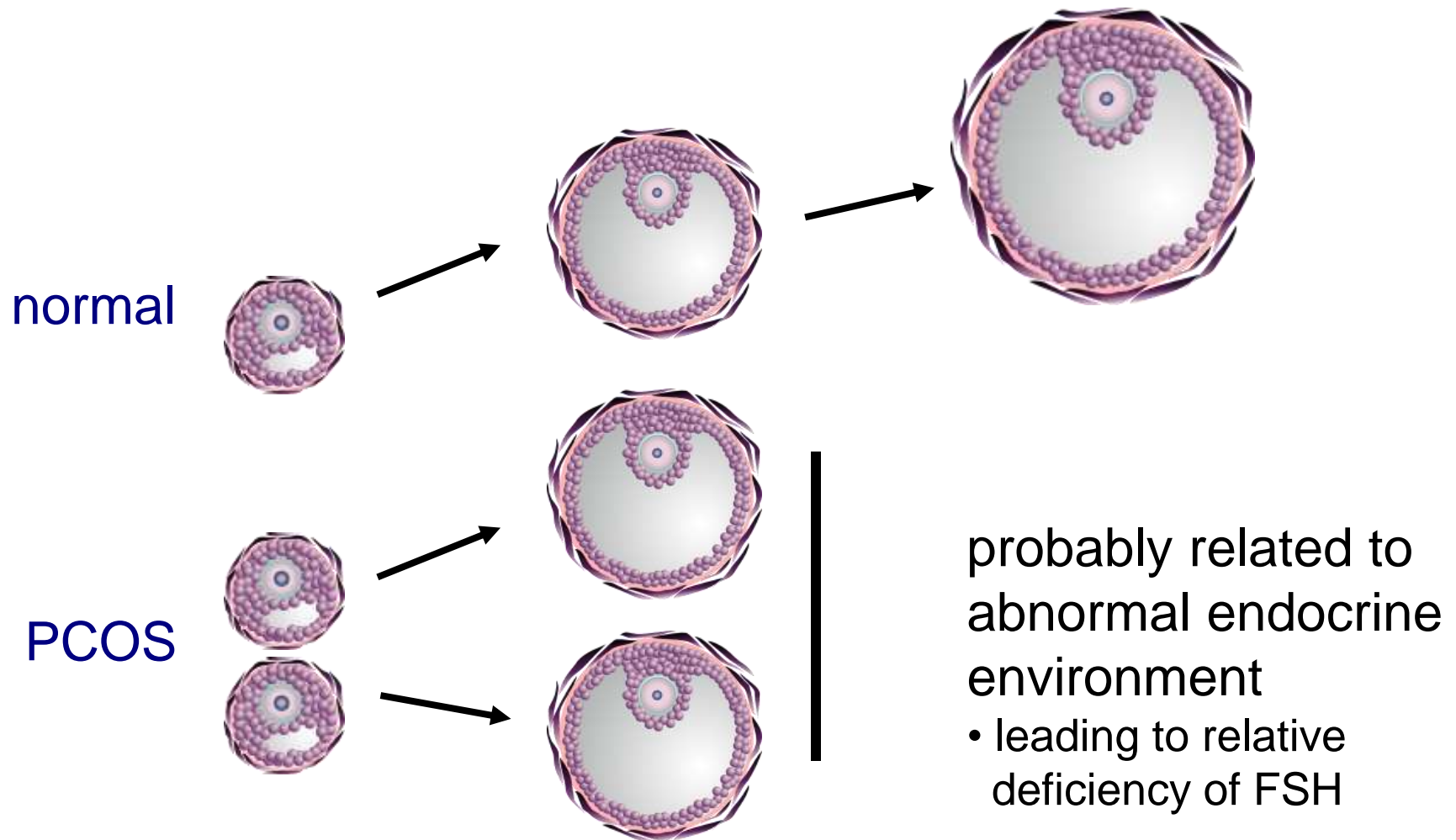
- Treatment of symptoms of anovulation
 - Regulate menses
 - Induce ovulation
- Treatment of symptoms of hyperandrogenism (hirsutism, acne, alopecia)
 - Hair removal
 - Eflornithine
 - COC, antiandrogens
- Treatment of obesity and metabolic disorders

Infertility in PCOS

- Major cause is infrequent or absent ovulation
- Other factors (eg endometrial) may play a role but this is a minor one

- Women with PCO and regular cycles do not have reduced fertility
- Risk of miscarriage is no higher in PCOS (or PCO) than in the general population

Arrested antral follicle development in PCOS



Will metformin help?

- It might!
- Cycles might be a bit more regular and ovulation more frequent
- Useful if you are not in a hurry to conceive

Induction of ovulation and superovulation

- Aim of *induction of ovulation* is to restore physiological (single follicle) ovulation in anovulatory women
- Aim of *superovulation* is to override physiology and stimulate multiple follicle development for IVF

The aim: single follicle ovulation



Clomiphene citrate and induction of ovulation in PCOS

- Treatment of first choice for induction of ovulation in PCOS
- Five day course of tablets; few side effects
- 75-80% ovulatory rate
- Cumulative conception rate similar to normal in ovulatory women
- Multiple pregnancy around 10%
- Ultrasound monitoring important in first cycle
- Non-responders can be treated by gonadotropins or laparoscopic ovarian diathermy

Management of hirsutism

Treatment of symptoms of hyperandrogenism

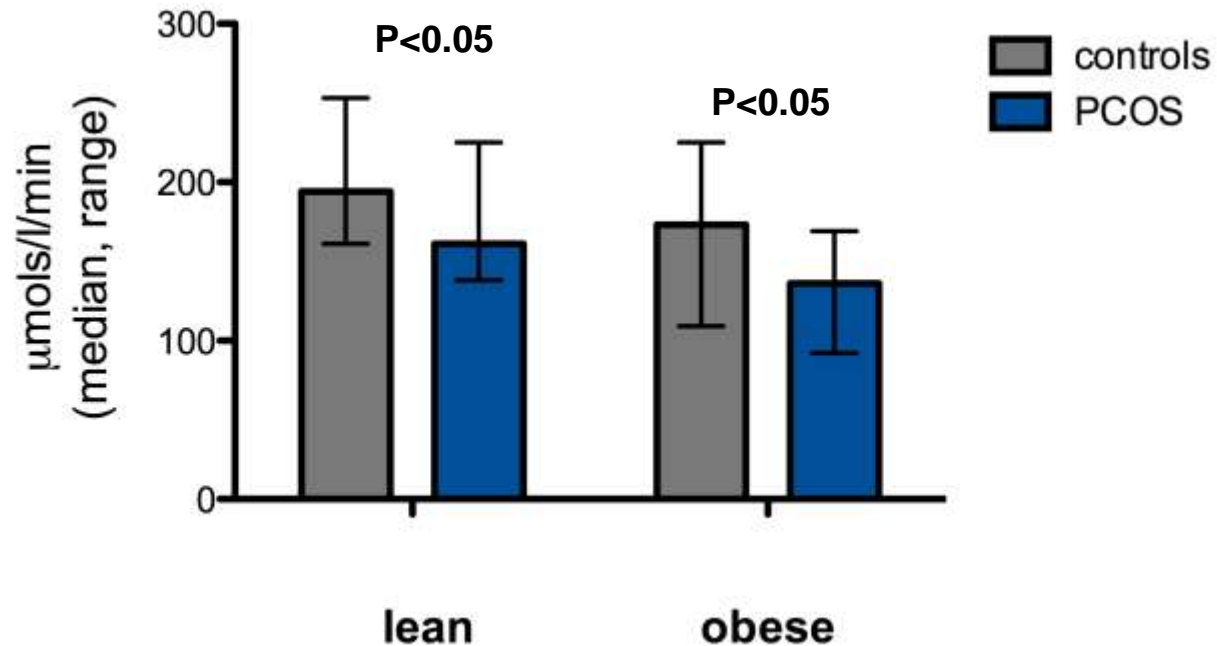
- Hirsutism
 - Hair removal (creams, shaving, electrolysis, laser)
 - Suppression of androgen secretion and/or action
 - oral contraceptives
 - anti-androgens: cyproterone acetate (including Dianette*); spironolactone; [flutamide]
 - 5α reductase inhibitors: finasteride
 - Topical inhibition of hair growth
 - eflornithine
- Acne
 - antibiotics; anti-androgens; roacutane
- Alopecia
 - anti-androgens; iron

Koulouri & Conway, *Bmj* 2009 338 b847

Franks, Layton & Glasier *Hum Reprod* 2008 23 231-2

Metabolic abnormalities and long-term health risks in PCOS

Insulin sensitivity is reduced in lean and obese women with PCOS



Dunaif *et al*, *Diabetes* 1989 38 1165-74.
Robinson *et al*, *Clin Endocrinol* 1992 36 537

Long-term consequences of metabolic dysfunction in PCOS

What are we worried about?

- Impaired glucose tolerance (IGT)
- Diabetes of pregnancy (GDM)
- Type 2 diabetes mellitus (T2DM)
- Cardiovascular disease (CVD)

Long-term consequences of metabolic dysfunction in PCOS

What are we worried about?

- Impaired glucose tolerance (IGT)
- Diabetes of pregnancy (GDM)
- Type 2 diabetes mellitus (T2DM)
- Cardiovascular disease (CVD)

and who are we worried about?

Gestational diabetes in women with PCOS

- High prevalence (52%) of polycystic ovaries in women with history of GDM
 - Kousta *et al*, *Clin Endocrinol* 2000 **53** 501-7
- Women with PCOS at increased risk of GDM (OR 2.94 (1.7 - 5.1))
 - Boomsma *et al*, *Hum Reprod Update* 2006 **12** 673-683 (meta-analysis)
- GDM in 22% of pregnancies in women with PCOS (*cf* expected prevalence of <5%)
 - De Wilde *et al*, *Hum Reprod* 2014 **29** 1327-36

Meta-analysis of studies reporting risk of Type 2 Diabetes in women with PCOS

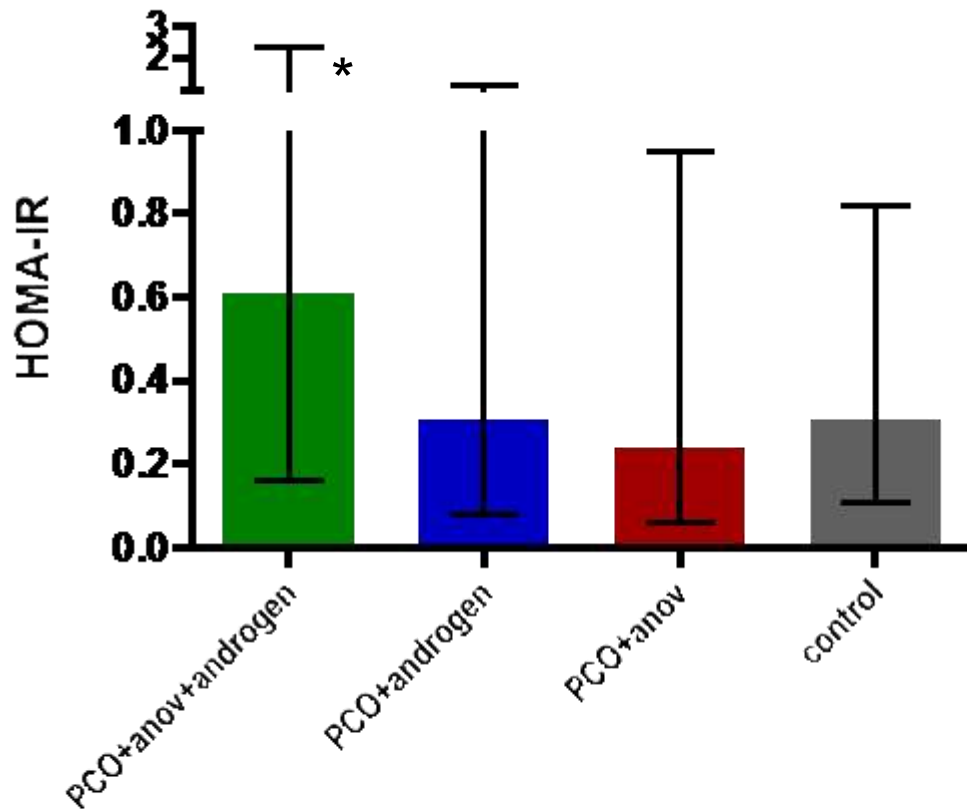
- IGT: OR 2.54 [1.44 - 4.47]
 - T2D: OR 4.00 [1.97 - 8.10]
- in BMI-matched groups

35 studies analysed

Moran et al Hum Reprod Update 2010 16 347-63

Insulin resistance is a feature of women who have *both* androgen excess and anovulation

HOMA-IR according to PCOS phenotype

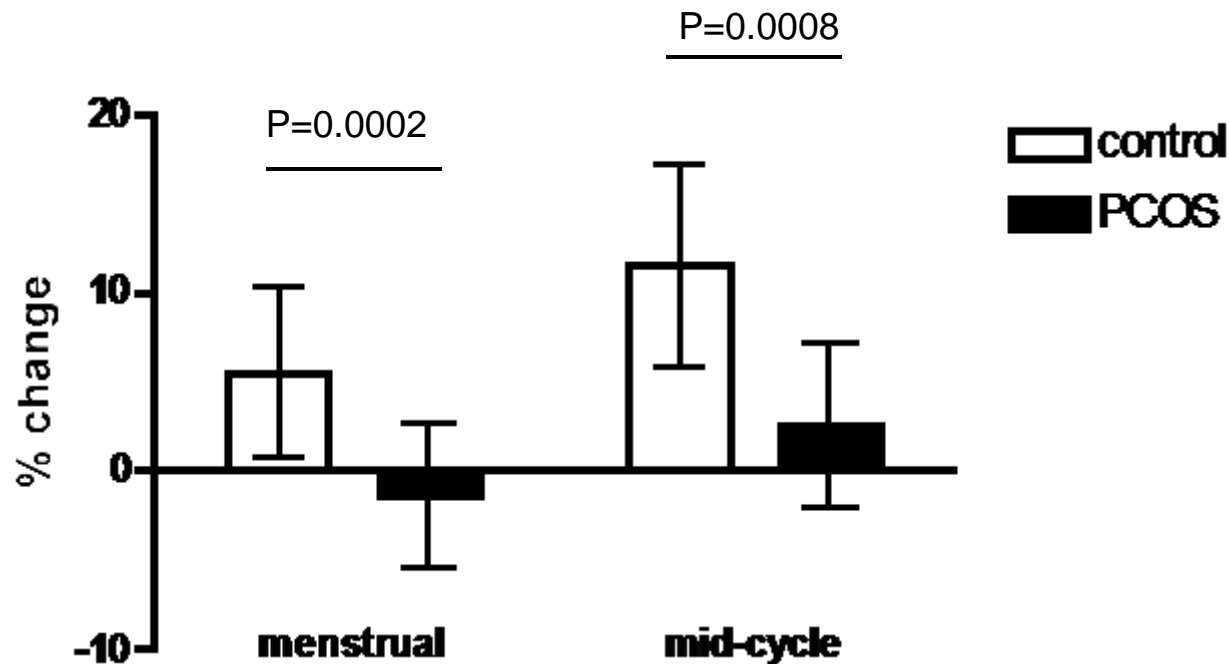


(Geometric mean ± SD)

PCOS and cardiovascular disease

Endothelial function (FMD) is significantly impaired in PCOS

...but is cardiovascular risk increased?



Fatal and non-fatal CHD in women with irregular cycles

	Regular	Usually irregular	Very irregular
RR (95% CI)	1.0	1.24 (1.04-1.44)	1.53 (1.24-1.90)

Nurses Health Study: 82,439 respondents re menstrual history at ages 20-35;
Follow up 14 years later (1417 incident cases of CHD)

Solomon C *et al*, *J Clin Endocrinol Metab* 2002 **87** 2013-7

PCOS and cardiovascular disease

BUT

- No conclusive evidence that women with PCOS are more likely to have CHD
- We lack longitudinal studies into 60s and beyond

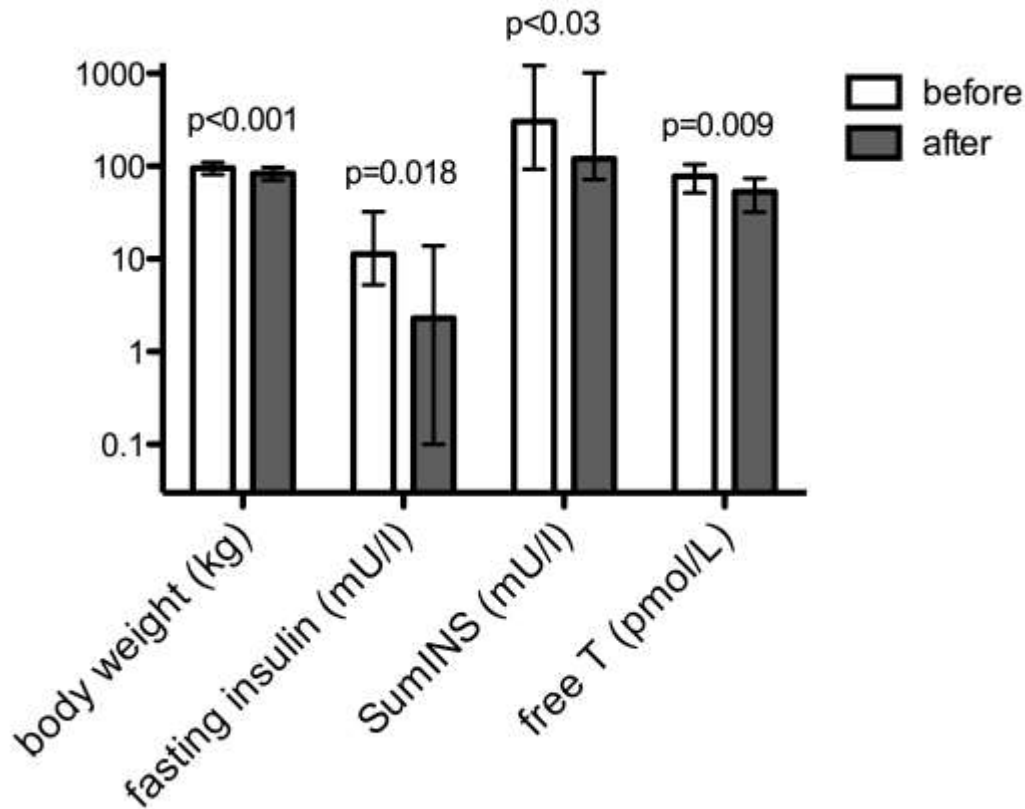
Screening for metabolic disorders in PCOS

- No test of insulin resistance is needed to make diagnosis of PCOS or to select treatment
- Obese women with PCOS (and/or those with abdominal obesity) should have an OGTT
- Utility of these tests in non-obese women with PCOS is not yet known

Prevention of diabetes in women with PCOS

- Make an *early* diagnosis
- Lean women with PCOS should not get fat
- Obese women with PCOS should be advised re diet and lifestyle
- Those at high risk may need need medication as well as lifestyle changes

Effect of diet/lifestyle on insulin and fertility in obese women with PCOS



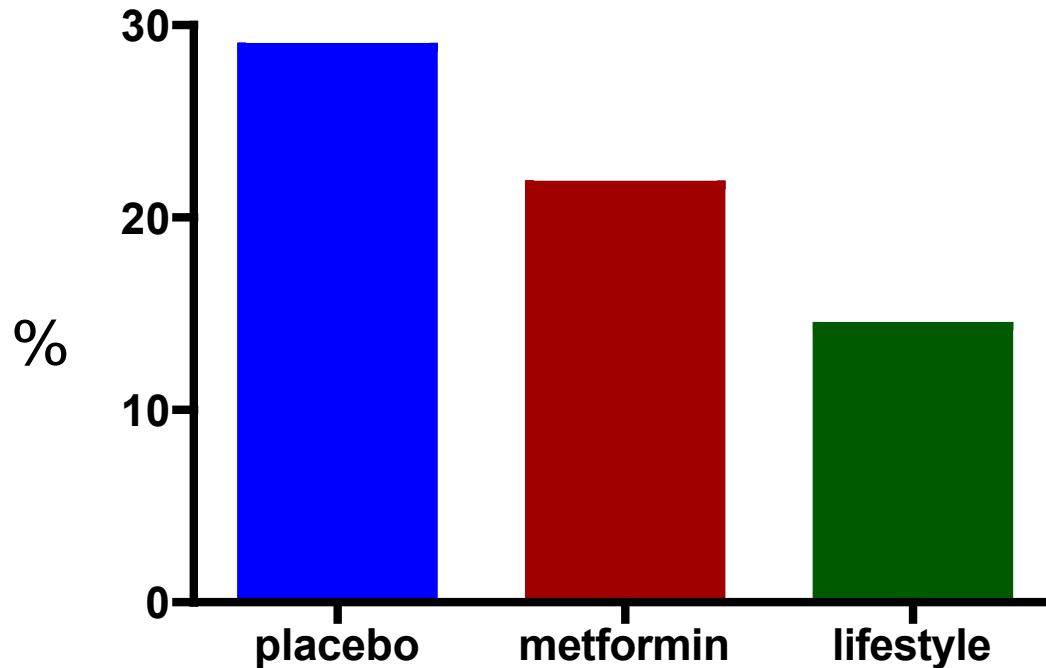
- modest (>5%) weight reduction associated with improvement in metabolic indices
- diet and lifestyle changes improve ovulation rate and fertility

(Kiddy *et al*, 1992; Clark *et al*, 1995; Norman *et al*, 2002; Steele *et al*, 2005; Moran *et al*, 2011)

Metformin in treatment of PCOS

- *Not* very useful for treatment of infertility or menstrual disturbances
 - Cycles might be a bit more regular and ovulation more frequent
 - Useful if you are not in a hurry to conceive
- *Not* very effective for treatment of hirsutism
- *Does* have a place in management of women at high risk of developing diabetes

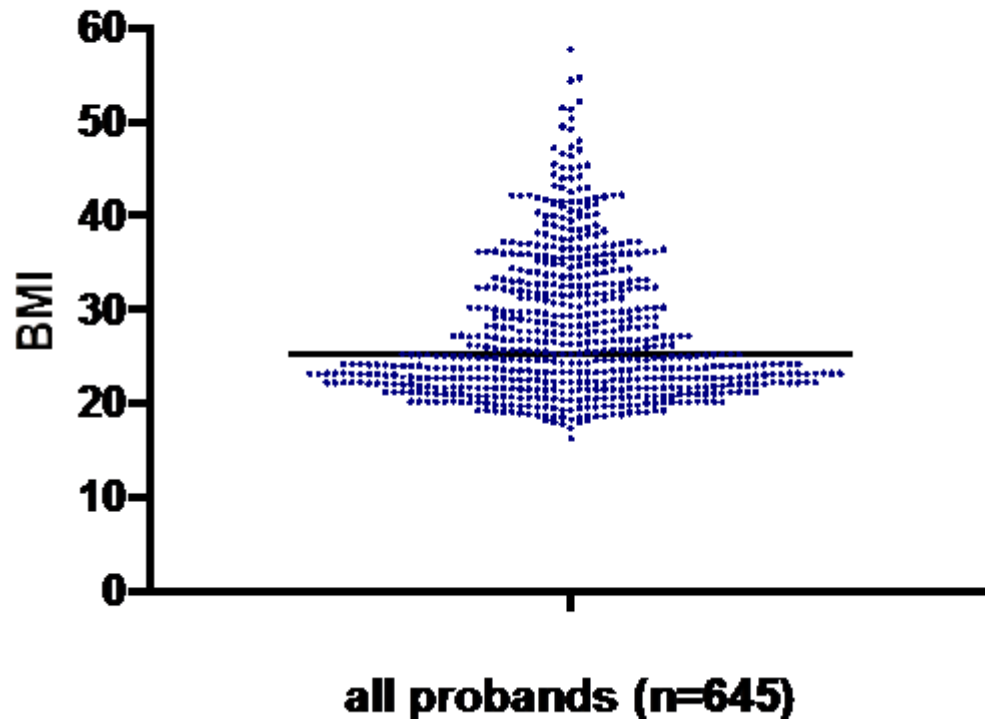
Cumulative incidence of T2D at 3 years



3234 subjects with IGT

Knowler WC *et al* Diabetes Prevention Program Research Group
N Engl J Med 2002 346 393-403

Not all PCOS patients are obese



Management of lean women with risk factors?

Role of thiazolidinediones (glitazones) in PCOS

- Improvement in insulin sensitivity, androgens and cyclicity
- Lipids not significantly altered and weight increased
- Concern about safety, particularly in women of reproductive age

Utility of GLP agonists, inositols?

Long term management of obese women with PCOS

- Diet and lifestyle changes improve ovulation rate, fertility and metabolic risk factors

but

- Weight reduction is rarely sustained
- Medication may be ineffective

The answer

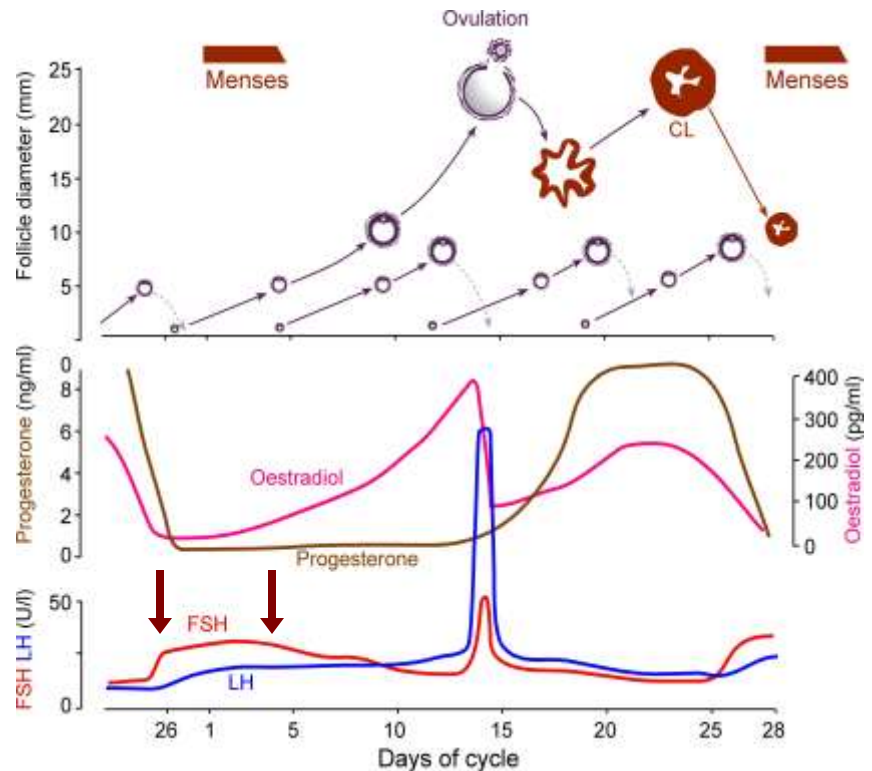
- **Bariatric surgery** may produce impressive improvements but should be one option offered by a **multi-disciplinary team** (metabolic physicians, bariatric surgeons, nurse specialists, dietitians, psychologists)
- **Prevention** of obesity is the best option of all – early intervention is very important

Summary

- PCOS is a very common endocrine problem
 - major cause of menstrual disturbance, subfertility, hirsutism
 - has implications for long term health
- Endocrine and metabolic features
 - typically raised serum testosterone, LH
 - insulin resistance a feature of some but not all women
- Investigation
 - small number of investigations needed
 - guided by clinical presentation
- Common management issues
 - effective control of symptoms during reproductive years
 - attention to long term health

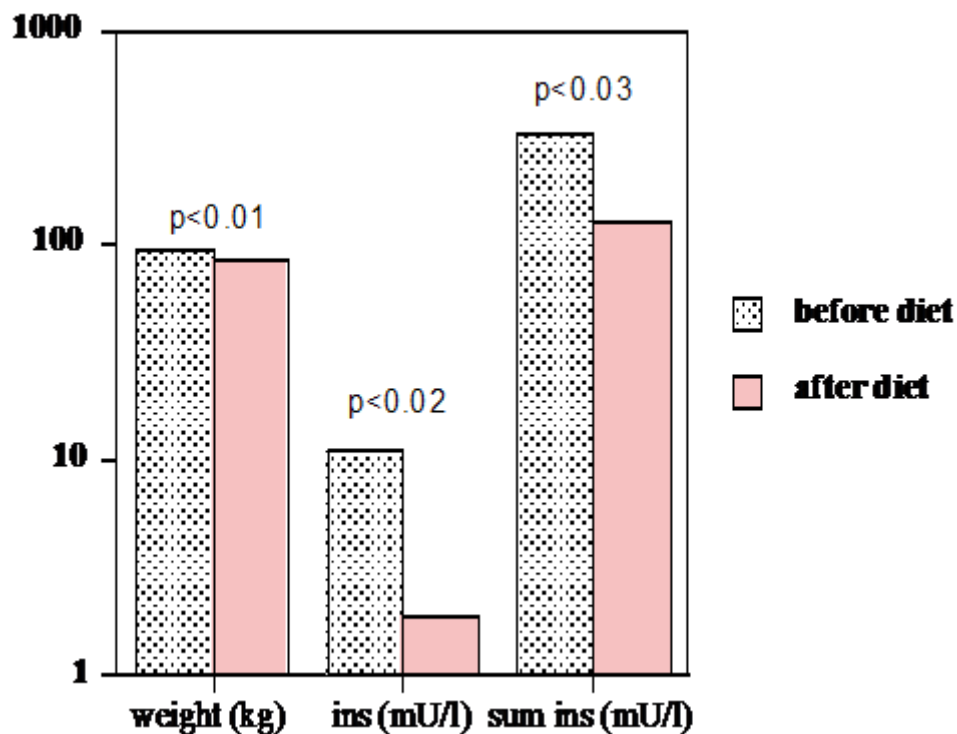
FSH concentrations are inappropriately low in anovPCOS

- Oestradiol and progesterone concentrations higher in anovPCOS than in early follicular phase
- Results in suppression of FSH and arrest of follicle maturation (Chavez-Ross *et al*, *J Math Biol*, 1997 36 95-118)



From Baird, 1983

Effect of calorie restriction on insulin and fertility in obese women with PCOS



- modest (5-10%) weight reduction associated with vast improvement in metabolic indices
- diet and lifestyle changes improve ovulation rate and fertility (Kiddy *et al*, 1992; Clark *et al*, 1995; Norman *et al*, 2002; Steele *et al*, 2005)

Metformin in treatment of PCOS

- Small number of properly-conducted clinical trials
 - Significant but very modest increase in ovulation rate
 - Questionable effect on unwanted body hair (no data on acne)
 - *No effect independent of weight loss on ovulation rate (Tang et al, Hum Reprod 2006 21 80–89)*
- Efficacy and indications for treatment unclear
- Large clinical trials (and review of evidence) suggest that the usefulness of metformin has been overestimated

(Tang et al, *Cochrane Database Syst Rev* 2010 Issue 1. Art. No.: CD003053. DOI: 10.1002/14651858)

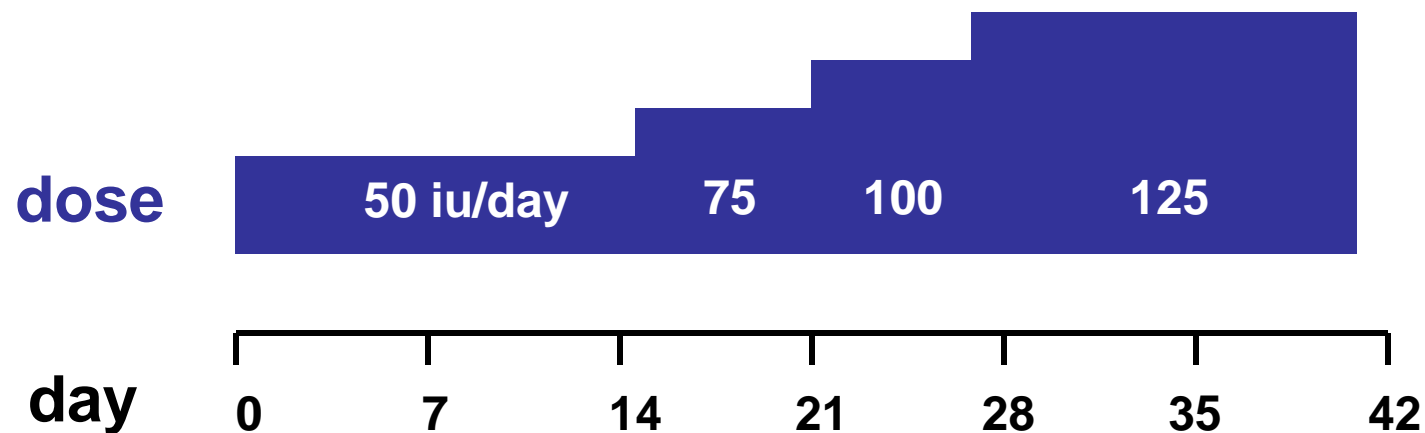
Metformin and clomiphene in treatment of PCOS

<i>Legro et al</i>	<i>clomiphene + metformin (209)</i>	<i>clomiphene + placebo (209)</i>	<i>metformin + placebo (208)</i>
Conception rate (%)	38.3	29.7	12.0
Live birth rate (%)	26.8	22.5	7.2

Moll *et al*, *BMJ* 2006, 332 1485-8

Legro *et al*, *New Engl J Med* 2007 356 551-66

Low-dose, “step-up” FSH regimen



Patient population

- 199 women with PCOS
- Age 30.3y (20-42); BMI 24.2 (18-45)
- Chronic anovulation; oestrogen-replete amenorrhoea or oligomenorrhoea
- No ovulation after clomiphene or no pregnancy after ≥ 6 ovulatory cycles

Outcome of treatment with low-dose FSH in 199 women

Cycles		916
Ovulatory cycles	657	(72%)
Uniovulatory cycles	562	(86%)
Pregnancies	91	(46%)
Miscarriages	21	(23%)
Multiples (all twin)	3	(3%)

mild "OHSS" in 4% of cycles

Fertility in women with PCOS a population study

- North Finland Birth Cohort (NFBC)
 - 4535 women born in 1966
 - 1103 (24%) had oligomenorrhoea and/or hirsutism
- Study of reproductive history at age 31

Koivunen, Pouta, Franks *et al*, *Hum Reprod* 2008 23:2134-39

NFBC fertility study

- Women with symptoms of PCOS
 - Suffered more frequently from infertility (26% vs 17%, $p < 0.01$)
 - Had reduced fecundability (time to 1st pregnancy increased)

NFBC fertility study

- Women with symptoms of PCOS
 - Suffered more frequently from infertility (26% vs 17%, $p < 0.01$)
 - Had reduced fecundability (time to 1st pregnancy increased)

BUT

- Overall pregnancy rate was similar in both “PCOS” and non-PCOS groups (76% vs 78%)
- Miscarriage rate was similar
- Number of pregnancies and family size were similar

- Infertility rate higher in the obese PCOS group than in obese controls (38% vs 16%, $p=0.001$)

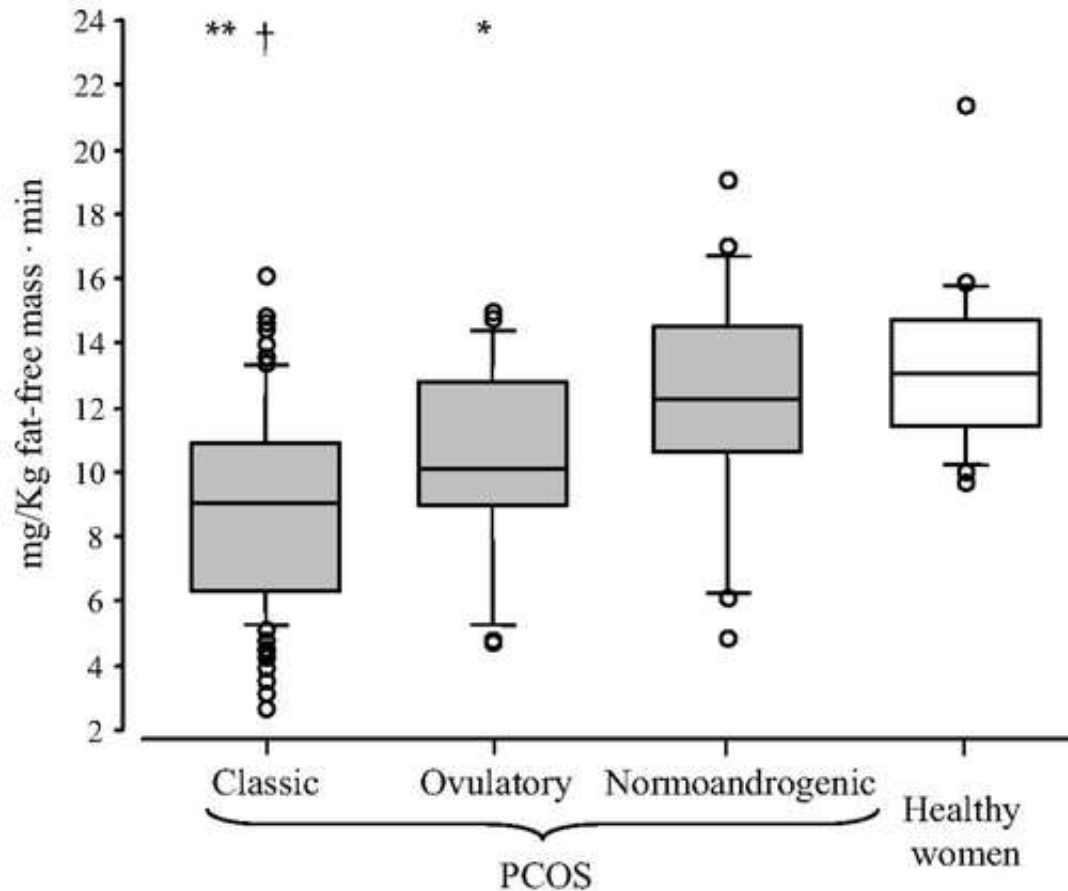
Follow-up of NFBC cohort at age 45

- Women with symptoms of PCOS were treated more often for infertility (6.1 vs 2.4%)
- Women with PCOS delivered one child as often as the reference population (75 vs 79%) and at a similar age
- but had slightly smaller family size (1.9 vs 2.4 children)
- Obese women with PCOS had fewer children than obese women with no symptoms (1.7 vs 2.6)

Polycystic ovary syndrome and fertility: Summary

- Infertility is due to infrequent or absent ovulation
- It is more common in overweight or obese women
- It can be treated successfully in most cases by diet, clomiphene (letrozole) or FSH
- Diet and lifestyle changes improve fertility in overweight women with PCOS
- Metformin is not first choice fertility treatment but may improve frequency of ovulation slightly
- Most women with PCOS have normal or slightly smaller family size

Insulin resistance (“clamp” studies) in subgroups of women with PCOS



137 women with PCOS (Moggetti *et al JCEM* 2013 98 E628-37)